Presentation, Etiology and Risk Factors in Patients with Focal and Segmental Glomerulosclerosis

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Certificate

This is to certify that "Presentation, Etiology and Risk Factors in Patients with Focal and Segmental Glomerulosclerosis" which is submitted as thesis requirement of the DM Branch III examination of the Dr. MGR Medical University is the bonafide work of the candidate:

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Objectives:

To identify prognostic factors that predict the risk of progression of renal failure in adult patients at the time of diagnosis of primary focal and segmental glomerulosclerosis (FSGS) and to calculate cumulative renal survival rate based on identified factors.

Focal and segmental glomerulosclerosis (FSGS) is defined as a clinical-pathologic syndrome manifesting proteinuria, usually of nephrotic range, associated with lesions of focal and segmental glomerular sclerosis and foot process effacement. Although hyaline insudation is common, the condition lacks glomerular immune complex deposits. Early in the disease process, the pattern of glomerular sclerosis is focal, involving a subset of glomeruli, and segmental, involving a portion of the glomerular tuft. As the disease progresses, a more diffuse and global pattern of sclerosis evolves. Alterations of the podocyte cytoarchitecture constitute the major ultrastructural findings.

FSGS came to be viewed as a distinct pathologic entity by 1970. In recent years it has become clear that FSGS is seen more usefully as a clinicopathologic syndrome, comprising diverse distinct diseases with different etiologies. These include genetic mutation (likely showing both Mendelian and non-Mendelian modes of inheritance), viral infection, relative overabundance of a pathogenic plasma factor, and hyperfiltration injury. Doubtless, there are other disease entities within the FSGS syndrome that remain undefined.

Among the biopsy proven renal disease in adults, focal and segmental glomerulosclerosis is the commonest histological category in all age groups (16.8%)[1]. Although the pathogenesis of primary focal and segmental glomerulosclerosis (FSGS) is unknown, it is one of the most common causes of primary glomerular disease that terminate in end stage renal disease (ESRD). In most series, the 10-year survival is between 40-60%.[2-5]

Various studies have shown that clinical, biochemical and pathological indicators can help to predict renal failure in a patient with FSGS. These are age at the time of

presentation, gender, amount of proteinuria, hypertension, renal dysfunction, percentage of sclerosed glomeruli and interstitial fibrosis, location of segmental sclerosis and therapeutic response to steroids[6,7]. Whether these prognostic factors and survival rate mentioned in the western literature are relevant to Indian population is unknown.

In the present study, we analysed the clinical, laboratory, and histopathological data of adult patients with biopsy proven FSGS over 10 years to identify risk factors at diagnosis associated with progression and to determine survival rates.

Fahr (1925) showed that patients with lipoid nephrosis who progressed to renal failure showed focal glomerular damage. Rich (1957) examined autopsy tissue from 20 children with nephrotic syndrome and otherwise typical lipoid nephrosis and described progressive sclerosis of glomeruli, affecting first the juxtamedullary glomeruli. McGovern (1964) and Hayslett et al[8] (1969) showed that in some patients whose initial biopsy examination showed minimal changes, a later biopsy examination showed focal sclerosing glomerulonephritis. Churg et al[9] (1970), writing for the International Study of Kidney Disease in Children, described biopsy examination findings in 127 children with nephrotic syndrome and found that focal sclerosing glomerular lesions were the second most common finding, after minimal changes.

The diagnosis of FSGS is complicated by the existence of a primary (or idiopathic) form and many secondary forms. Secondary FSGS caused by structural-functional adaptations mediated by intrarenal vasodilatation and by increased glomerular capillary pressures and plasma flow rates. Such maladaptive glomerular hemodynamic alterations can arise through: (1) a reduction in the number of functioning nephrons (such as after unilateral renal agenesis, surgical ablation, oligomeganephronia, or any advanced primary renal disease), or (2) mechanisms that place hemodynamic stress on an initially normal nephron population (as in morbid obesity, cyanotic congenital heart disease, and sickle cell anemia). Finally, primary and secondary FSGS also must be differentiated from the nonspecific pattern of focal and segmental glomerular scarring that can follow a variety of inflammatory, proliferative, thrombotic, and hereditary conditions.

Table 1. Etiologic Classification of FSGS

Primary (idiopathic) FSGS

C1q nephropathy

HIV-associated nephropathy

Heroin nephropathy

Familial FSGS

- Mutations in α-actinin 4 (autosomal dominant)
- Mutations in podocin (autosomal recessive)
- Mitochondrial cytopathies

Drug toxicity

- Pamidronate
- Lithium
- Interferon-α

Secondary FSGS

- Reduced renal mass
  - Oligomeganephronia
  - Unilateral renal agenesis
  - Renal dysplasia
  - Reflux nephropathy
  - Sequela to cortical necrosis
  - Surgical renal ablation
  - Any advanced renal disease with reduction in functioning nephrons
  - Chronic allograft nephropathy
- Initially normal renal mass
  - Diabetes mellitus
  - Hypertension
  - Obesity
  - Cyanotic congenital heart disease
  - Sickle cell anemia

Nonspecific pattern of FSGS caused by renal scarring

- Focal proliferative glomerulonephritis (IgA nephropathy, lupus nephritis,etc)

Hereditary nephritis
Diabetic nephropathy
Hypertensive arterionephrosclerosis
Membranous glomerulopathy
Thrombotic microangiopathies

Pathologic Classification:

FSGS comprises a number of morphologic subtypes that may have different prognostic and therapeutic implications. These morphologic variants were defined at a recent consensus conference of renal pathologists in New York City.

FSGS not otherwise specified (NOS) constitutes the generic lesion of FSGS. The synonyms classic FSGS or FSGS of the usual type often are applied. This category requires that other morphologic categories (perihilar, cellular, tip, and collapsing) be excluded. FSGS (NOS) is the most common morphologic pattern of FSGS. Evidence from repeat biopsy examinations suggests that other variants may evolve into this pattern in the course of disease progression and increasing chronicity.

Morphologically FSGS (NOS) is characterized by Lesions of sclerosis can affect the perihilar (ie, vascular pole) region or the periphery of the tuft. In some glomeruli, segmental lesions may affect more than one lobule, involving both the perihilar and peripheral regions. According to one study using serial sections, peripheral lesions tend to be more common in childhood FSGS than the adult disease.[10] Any number of glomeruli can be affected by segmental sclerosis, with or without associated global sclerosis. There may be segmental glomerular basement membrane collapse without podocyte hyperplasia.

By immunofluorescence, there is typically focal and segmental granular deposition of IgM, C3, and more variably C1 in the distribution of the segmental glomerular sclerosis and hyalinosis . More generalised weak mesangial deposition of IgM also may be present.

By electron microscopy, the lesion of segmental sclerosis display wrinkling and retraction of glomerular basement membrane and accumulation of inframembranous hyaline, with resulting narrowing or occlusion of the glomerular capillary lumina. The electron dense hyaline material is usually more waxy in appearance than true immune complex deposits and tends to pool beneath the GBM, conforming to the contours of the delimiting membrane. Endocapillary foam cells appear as large intracapillary cells containing abundant electron lucent vacuoles.

Directly overlying the lesions of segmental sclerosis there usually is complete effacement of foot processes, accompanied by podocyte alterations that include hypertrophy, increased organellar content, and focal microvillous transformation. This microvillous appearance is caused by the formation of slender cellular projections resembling villi along the surface of the podocytes facing the urinary space. The hypertrophied podocytes display rounded cell bodies that adhere smoothly to the glomerular basement membrane (GBM), with frequent loss of primary processes.

The major ultrastructural finding involving nonsclerotic glomerular capillaries is foot process effacement. The degree of foot process fusion observed overlying these open capillaries varies from mild to severe, but usually involves greater than 50% of the total

glomerular capillary surface area. In general, the degree of fusion correlates roughly with the severity of the proteinuria, such that patients with subnephrotic proteinuria tend to have less foot process fusion than those who are fully nephrotic. In the areas of foot process effacement, there usually is loss of recognizable slit diaphragms and mat-like condensations of cytoskeletal filaments oriented parallel to the direction of the GBM itself. Thus, although the lesions of FSGS are focal at the light microscopic level, the podocyte alterations are relatively diffuse at the electron microscopic level

FSGS perihilar variant category requires that the cellular variant, tip variant, and collapsing variant be excluded. It is defined by the presence of perihilar sclerosis and hyalinosis involving greater than 50% of segmentally sclerotic glomeruli. Glomerulomegaly and adhesions are common. Podocyte hypertrophy and hyperplasia may be present but typically are less frequent than in the other variants. Other glomeruli may show lesions of segmental and/or global glomerulosclerosis, as described for FSGS (NOS) earlier.

Perihilar variant of FSGS may occur in primary FSGS. However, when accompanied by glomerulomegaly, it is particularly common in patients with secondary forms of FSGS mediated by an adaptive response to increased glomerular capillary pressures and flow rates (as in association with obesity, cyanotic congenital heart disease, reflux nephropathy, renal agenesis, dysplasia, oligomeganephronia, or any advanced renal disease with a reduced number of functioning nephrons).

The cellular variant of FSGS was first described by Schwartz and Lewis in 1985. The cellular variant is defined by the presence of at least one glomerulus with segmental endocapillary hypercellularity involving at least 25% of the tuft and causing occlusion of the capillary lumen. Any segment (perihilar or peripheral) may be affected. When numerous glomeruli are affected, the process may mimic focal proliferative glomerulonephritis.[11]

By immunofluorescence there is focal and segmental glomerular positivity for IgM and C3. At the ultrastructural level, the cellular variant usually displays severe foot process effacement, correlating with the generally high levels of proteinuria . Cellular lesions consist of segmental occlusion of glomerular capillaries by endocapillary hypercellularity including foam cells and monocytes. The glomerular basement membrane is intact, without evidence of rupture.

Compared with FSGS (NOS), the cellular variant is characterized by more severe proteinuria and a shorter time course from clinical onset of renal disease to biopsy examination, suggesting an early phase in the evolution of the segmental sclerosis. Schwartz and Lewis found a shorter interval between onset of proteinuria (3.4 versus 71.9 mo) in patients with cellular versus classic FSGS. Moreover, 90% of patients in the cellular group had urine protein levels greater than 3 g/d, compared with 49% of those without cellular lesions. Similarly, the incidence of full nephrotic syndrome at presentation was significantly higher (70% versus 23%). Patients with cellular FSGS often have a very abrupt onset of severe nephrotic syndrome

The cellular variant may be responsive to immunosuppressive therapy.[12] This favourable treatment response probably relates to the early and relatively active stage of glomerular injury in the cellular variant.

The tip variant of FSGS is defined by the presence of at least one glomerulus with a segmental lesion involving the tip domain (ie, the peripheral 25% of the glomerular tuft next to the origin of the proximal tubule). There must be either adhesion between the tuft and Bowman's capsule at the tubular lumen or neck, or confluence of podocytes with parietal epithelial or tubular epithelial cells at the tubular pole or neck.

Tip lesions may arise as a nonspecific response of the peritubular segment of the glomerular tuft to fluxes of protein-rich filtrate in the setting of nephrotic syndrome.

The designation of collapsing variant is applied to cases of FSGS in which at least one glomerulus displays segmental or global obliteration of the glomerular capillary lumina by wrinkling and collapse of GBMs associated with podocyte hypertrophy and hyperplasia. Collapse involving a single glomerulus is considered significant, such that the presence of any glomerular collapse pre-empts the other morphologic categories of FSGS.

There are 2 pathologic findings that together define the collapsing variant of FSGS.[13,14] First, there is implosive wrinkling and retraction of the GBM. Second, there is marked hypertrophy and hyperplasia of overlying visceral epithelial cells. Visceral

epithelial cells frequently contain protein resorption droplets and may appear detached from the underlying GBM. Lesions of collapsing FSGS often coexist in the same biopsy specimen with other patterns of FSGS, including cellular lesions and discrete segmental scars typical of the classic form of FSGS.

The changes seen in collapsing FSGS are not confined to glomeruli. There are typically widespread tubular degenerative changes including luminal ectasia, cytoplasmic simplification and vacuolization, loss of brush border, nuclear pleomorphism with prominent nucleoli, and multiple mitotic and apoptotic figures. Proximal tubules also display protein resorption droplets. In almost half of cases, tubular microcysts are seen and typically display a proteinaceous filtrate that stains positively with the periodic acid Schiff stain. Interstitial edema and a mild to moderate chronic inflammatory infiltrate characteristically accompany the tubular degenerative changes. Rare foci of mild tubulitis may be apparent. With progression of disease, tubular atrophy and interstitial fibrosis intervene.

In the setting of collapsing FSGS, immunofluorescence typically reveals positivity for IgM and C3 in the distribution of the lesions of FSGS. The intensity of staining is typically trace to 1+ but may be up to 2+ (scale: 0, trace, 1-3+). Staining for IgG, IgA, and κ and λ light chains is negative.

Electron microscopy reveals an increase in the number and size of podocytes. On the subcellular level, there may be an increase in organellar content and transport

vesicles, microvillous transformation, lipid and protein resorption droplets, and extensive foot process fusion. Although the podocyte changes normally are diffuse, glomeruli containing lesions of collapsing FSGS will display more prominent podocyte changes as well as wrinkling and retraction of the GBM. Within the capillary lumina, focal hyaline insudation and rare endocapillary foam cells may be apparent. Electron dense deposits typically are absent although rare mesangial deposits should not be a deterrent from making the diagnosis of collapsing FSGS.

Trends in the Epidemiology of FSGS:

FSGS is currently a leading cause of nephrotic syndrome in adults. Previous studies from the 1970s and early 1980s list FSGS as being responsible for 15% to 20% of cases of idiopathic nephrotic syndrome (NS) in adults. Korbet et al[15] found that among primary renal diseases, FSGS accounted for 29% of all adult patients presenting with nephrotic range proteinuria between 1975 and 1985, but accounted for 38% of such patients between 1985 and 1994. Hass et al also observed similar increases in the proportion of FSGS in adults undergoing a biopsy examination for proteinuria or nephrotic syndrome.[16] The incidence of FSGS as a cause of end-stage renal disease (ESRD) also is increasing. The increase in the fractional contribution of FSGS to the etiology of primary nephrotic syndrome could also be caused by changes in the demographics of patients undergoing renal biopsy examinations or a decline in the incidence of other diseases such as membranous glomerulopathy or minimal change disease.

Racial background has a strong influence on the propensity to develop FSGS. Black subjects have an increased risk for idiopathic FSGS, as has long been recognized.[17] In a logistic regression analysis of adult patients with nephrosis, race remained the only significant predictor for FSGS, with black subjects 4 times more likely to have FSGS than white subjects. Black individuals are also at increased risk for Human immunodeficiency virus (HIV)-associated FSGS.[18] Occult HIV infection is unlikely to explain the increasing frequency of FSGS. Although screening for HIV is often not performed in patients with glomerulonephritis, most studies that show an increasing incidence of FSGS in black individuals exclude patients with known HIV, intravenous drugs usage, or the presence of tubuloreticular structures. In at least one study with serologic testing for HIV, a high frequency of idiopathic FSGS also was shown in black subjects. Other infectious agents such as parvovirus B19[19]and SV40[20] have been linked to the development of FSGS. Whether these viruses or other as yet unknown infectious agents may contribute to the increasing occurrence of FSGS in susceptible populations is yet to be determined.

Another consideration is the increase in the collapsing variant of FSGS. Barisoni et al[21] found an increasing incidence of FSGS with collapsing features among HIV-negative patients. This entity was not seen before 1979 and has more than doubled from 11% of all idiopathic FSGS between 1979 and 1985 to 24% from 1990 to 1993. The same group found that patients with collapsing FSGS were predominantly of black race. The median renal survival from time to biopsy examination to end stage renal disease was shorter in the collapsing group (13 mo) compared with the other FSGS group (63 mo). Other investigators confirmed the higher incidence of the collapsing variant in black subjects and the poor renal outcome associated with this condition.[22] However, these investigators reported that the collapsing variant only accounted for 4% of all FSGS and the number of cases did not increase with time. These discordant findings may be owing to differences in case definition or true population differences. Because of its rapid

progression to renal failure, the collapsing variant likely contributes disproportionately to the FSGS patients reaching end stage kidney disease. This may in part account for a higher incidence of black subjects with FSGS end stage renal disease.

Genetic Basis of FSGS:

The role of genetic factors in the development of FSGS in humans has become increasingly apparent in recent years. Genetic studies also have helped strengthen the notion that glomerular visceral epithelial cell (or podocyte) disorders lead to a spectrum of clinical presentations, from congenital nephrotic syndrome (CNF), to minimal change disease (MCD), and FSGS. Four siblings with nephrotic syndrome were described in a 1957 report. Pathology showed minimal change disease in some children, FSGS in others. The absence of disease in the parents suggested recessive inheritance. Additional scattered reports of both single-generation and multigeneration disease have continued to appear in the case literature.[24]

Congenital nephrotic syndrome of the Finnish type, or CNF, is a geographically widespread disease characterized by the development of severe nephrosis in utero and autosomal-recessive inheritance. Affected neonates have on the order of 20 to 30 g/d proteinuria and typically die from complications of the nephrotic syndrome at a young age. Subsequent to mapping the CNF gene to chromosome 19q13 by a means of a genome-wide linkage analysis, the CNF gene NPHS1 was cloned by positional methods. Nephrin, the gene product, is a 185-kd protein containing a fibronectin III-like domain, 8

immunoglobulin C2 motifs, and a single transmembrane segment. Nephrin localizes to the slit diaphragm in the podocyte. Nephrin appears to play a role in regulating signaling pathways.[25]

Most of the congenital nephrotic syndrome in Finland is caused by 2 specific NPHS1 mutations, Fin major (the deletion of nucleotides 121-122 leading to a frameshift) and Fin minor (encoding a premature termination signal at amino acid 1109). The incidence of CNF is 1 in 500 live births in this group.

The identification of NPHS1 has improved the antenatal diagnosis of CNF.

Fuchshuber et al described a form of nephrosis characterized by recessive transmission, early onset, resistance to steroid therapy, and rapid progression to end-stage kidney failure. The majority of the affected children showed an FSGS pattern on renal biopsy. The gene for this recessive form of FSGS was mapped to chromosome 1q25-31 and subsequently cloned. NPHS2, the responsible gene, encodes podocin, a 383 amino acid integral membrane protein.

Autosomal-dominant forms of FSGS typically present later and are more slowly progressive than recessive forms. Mutations in ACTN4, encoding α-actinin-4, cause a slowly progressive form of disease with dominant inheritance, nonnephrotic proteinuria, and renal insufficiency. The penetrance of ACTN4-associated disease is high but not 100%. ACTN4 is the only actinin expressed significantly in the human glomerulus. The

ACTN4 mutations identified in FSGS families are all missense and increase the affinity of the encoded protein to actin filaments.

FSGS also is seen as part of well-defined inherited syndromes. The spectrum of disease seen with WT1 mutations is the best studied of these disorders. Frasier syndrome and Denys-Drash syndrome are related and overlapping syndromes caused by mutations in WT1. Both syndromes are characterized by glomerular disease and the development of male pseudohermaphroditism.

Frasier syndrome is caused by donor splice mutations in intron 9 of WT1. Frasier syndrome can present as FSGS in 46, XX females in association with gonadal malignancy.[26,27]

Denys-Drash syndrome is defined by diffuse mesangial sclerosis on renal biopsy examination, genitourinary tumors, and pseudohermaphroditism. A different spectrum of mutations is seen in Denys-Drash syndrome, most commonly within exon 9 of WT1.[28]

Nail-Patella syndrome generally is regarded as a disease of the basement membrane rather than the podocyte, though it is probably both. An altered glomerular basement membrane typically predominates on histologic analysis, the glomerulopathy is variable and can present as nephrotic syndrome. Defects in the lmx1b transcription factor are responsible for disease. Lmx1b helps control the transcriptional regulation of matrix proteins by the podocyte as well as the podocyte genes CD2AP and NPHS2.

Permeability Factors in FSGS:

The theory that idiopathic nephrotic syndrome, minimal change nephrotic syndrome (MCNS) or FSGS represents “a systemic abnormality in lymphocyte function resulting in the secretion of a circulating chemical mediator toxic to an immunologically innocent glomerular basement membrane” was proposed formally by Shalhoub[29] in 1974. This proposal was based on the absence of evidence for a humoral antibody response, on clinical remissions after treatment with steroids or cyclophosphamide and after measles infection, and on the occurrence of nephrotic syndrome in patients with Hodgkin's lymphoma. The presence of a circulating factor in FSGS was proposed by Hoyer et al[30] after they observed that nephrotic proteinuria recurred promptly after transplantation of a normal kidney into a recipient who had FSGS as the cause for renal failure. This idea was supported by the observation of Zimmerman[31] that injection of serum from a patient with recurrent FSGS into the aorta of a rat resulted in an immediate onset of proteinuria and albuminuria. No proteinuria occurred after infusion of sera from a patient with prior FSGS but no posttransplant recurrence or from 10 patients with other forms of nephrotic syndrome. Treatment of patients with recurrent FSGS in renal allografts with plasmapheresis, immunoadsorption, or low-density lipoprotein apheresis may result in decreased proteinuria and prolongation of allograft survival.

Work to clarify the relationship of a circulating proteinuric factor to FSGS remained dormant until the early 1990s when seminal observations from several centers provided strong evidence that an etiologic factor was present in a number of patients with

recurrent FSGS. In 1994, Savin et al reported that incubation in medium containing serum or plasma from patients with recurrent FSGS increased albumin permeability (P_{alb}) of glomeruli isolated from normal rats and that the capacity to increase P_{alb} was reduced by plasmapheresis.[32,33] During that same year, other investigators reported that injection of eluate obtained from plasma of patients with recurrent FSGS and eluted from protein A-immunoadsorbent material induced albuminuria in rats.[34] In vitro testing using functional assays of permeability based on glomerular volumetric responses to oncotic gradients has been essential to understand the role of permeability factors in FSGS.

The mechanism by which the FSGS factor increases glomerular albumin permeability *in vitro* or *in vivo* remains to be elucidated. Increased glomerular albumin permeability after 10 min of incubation *in vitro* raises the possibility that the FSGS factor interacts with membrane components of the exposed glomerular epithelial cells. Glomerular epithelial cells have been shown to play a crucial role in maintaining the filtration barrier. The magnitude of the effect of FSGS sera on glomerular permeability *in vitro* was comparable to that of anti-Fx 1a antibody, superoxide, hydroxyl ion, or tumor necrosis factor α. The rapidity of increase in glomerular permeability suggests that the immediate effect of the FSGS factor is unlikely to be mediated by metalloproteinase-3 or through charge neutralization by protamine[35], as these agents required prolonged incubations of more than 4 h and 1 h, respectively.

It appears that the mechanism by which the FSGS factor increases glomerular permeability depends on active cellular metabolism rather than charge neutralization. This conclusion is based on the rapidity of the response, the small quantity of the FSGS factor required, its anionic rather than cationic charge, and the fact that a number of inhibitors prevent the increase in permeability. The mechanism that is most clearly documented relies on the action of cyclooxygenase. The permeability barrier is preserved by the inclusion of indomethacin or the thromboxane synthase inhibitor furegrelate in the incubation medium. Several eicosanoids increase P_{alb} including PGE_2, $PGF_{2\alpha}$, and a thromboxane A_2 mimetic.

Hyperfiltration and Glomerulosclerosis:

In 1932, Chanutin and Ferris described proteinuria and progressive glomerulosclerosis after major reductions in renal mass in the rat. Subsequent investigators, notably Shimamura and Morrison, further characterized the experimental disease of the remnant kidney using ultrastructural approaches and described fusion of epithelial cells as well as glomerular enlargement. Olson et al[36] further detailed the cellular and permselective responses, documenting detachment of podocytes from the basement membrane and loss of filtration size selectivity. These studies all used high degrees of subtotal renal ablation to induce injury in the remnant glomeruli. Others have shown a graded response to removal of kidney parenchyma with even lesser degrees of reduction accelerating damage but at a slower rate and with less severe damage. For example, even simple unilateral nephrectomy leads to an increased pace of sclerosis in remaining kidneys. With loss of renal tissue and before they sustain pathologic changes, the remaining nephrons undergo a process conventionally termed compensatory hyperfunction, whereby their single nephron filtration rates increase and the nephrons grow. The notion arose that this increase in single nephron filtration or hyperfiltration, though compensatory in the short term, caused subsequent pathology.

In humans, simple unilateral nephrectomy in otherwise healthy individuals seems to lead to little in the way of adverse renal consequences. Perhaps the most complete study is one of men who lost a kidney owing to trauma during World War II. When these people were followed-up 45 years later, no increase in renal disease, hypertension, or

proteinuria could be discerned. Furthermore, in a subset for whom autopsy tissue was available, no increased prevalence of glomerular injury was notable. As the investigators cautioned, these servicemen were largely of European ancestry and healthy at the time of their initial loss of a single kidney. However, reviews of individuals who have donated a kidney for transplantation have in general revealed no substantial long-term consequences. The donors were, of course, screened for serious underlying kidney disease or conditions predisposing to a renal injury. On the other hand, some suggestions that losses of renal mass perhaps at susceptible periods of development or in susceptible individuals may be associated with subsequent injuries have been recorded. For example, unilateral renal agenesis is a relatively rare congenital condition but it has been associated with serious proteinuria and sclerosis of the single kidney as an individual ages. Conceivably in this circumstance, the solitary kidney has subtle developmental defects that render it susceptible to injury. Likewise, progressive damage to the remaining kidney after removal of a contralateral diseased kidney may just reflect unrecognized bilateral disease. However, with more extreme renal surgery, injury may be seen in humans. One study of subtotal nephrectomy sustained owing to aggressive renal cancer surgery has suggested that sclerotic injury develops in the spared but hypertrophied glomeruli. Perhaps as in the animal studies, some variations occur among different groups of people and susceptibility to loss of renal mass may be more pronounced in some individuals.

Fairly wide variation in the number of nephrons has been noted in human adult kidneys. Given the general trend, at least in animal studies, for lesser nephron number to lead to greater single nephron filtration rate and greater propensity for injury, Brenner

and Mackenzie have argued that individuals with natively fewer nephrons are predisposed to renal disease, hypertension, and glomerular sclerosis. The concept fits in part with Osmond's and Barker's hypothesis that lower birth weights predispose to cardiovascular disease in later life.

The potential for glomerular capillary pressures to induce progressive sclerotic injury seems clear. Numerous studies have implicated all 3 of the major glomerular cell types in this process. Because of their similarities to vascular smooth muscle cells, which have vigorous responses to arterial hypertension, and because of the prominent mesangial abnormalities with hyperfiltration, investigators have focused on the mesangial cell's response to altered glomerular hemodynamics.

Mesangial cells, when grown in culture on a pliable matrix, proliferate in response to stretching. This model simulating increased glomerular tension displays, in addition to cellular hyperplasia, increased production of matrix substances such as collagens, laminin, and fibronectin. Cells along the periphery of cyclically stretched membranes, where deformation is most pronounced, develop the greatest degree of proliferation and matrix production. This finding further supports the view that increased physical stretching of the mesangial cells contributes to responses reminiscent of the fundamental processes of sclerosis in vivo

A series of events involving podocyte failure have been proposed by Kriz et al. These investigators have suggested that in the course of a hemodynamically induced

sclerosis, the failure of the mesangial cells to provide a tethering function to the overlying basement membrane in conjunction with podocyte insufficiency bares basement membrane, which provides not only an egress for protein, but also a point at which the parietal epithelial cells may adhere to this exposed basement membrane.

After these seemingly adaptive increases in function, pathologic changes appear, eventuating in glomerular sclerosis. Among the determinants of increased single-nephron filtration after renal mass reduction, the increase in glomerular capillary pressure seems to be pre-eminent in aggravating the progressive sclerotic changes. Actions of the renin-angiotensin-aldosterone system probably underlie many of these hemodynamic changes. Other vasoactive systems also are likely to exert actions in the process but no one element of these systems has yet proven to be a necessary component of heightened pressures. Various cellular responses follow from these higher glomerular pressures, especially in association with the hypertrophy of the glomerular unit. Changes in mesangial cell function, relative deficiency of podocytes, and perhaps endothelial generation of vasoactive and fibroproliferative cytokines, all have been linked in the chain connecting hemodynamic changes with glomerular sclerosis.

Human Immunodeficiency Virus (HIV) and FSGS:

Human immunodeficiency virus-associated nephropathy (HIVAN) was first described by Rao et al[37] in 1984 in 10 patients with acquired immune deficiency syndrome who developed a rapidly progressive renal disease. These patients had

moderate to massive proteinuria and all developed end-stage renal disease within 16 weeks. Biopsy examinations revealed focal segmental glomerular nephritis. Six of the 11 patients had no known risk factors for renal disease, and the association was made between infection with HIV-1 and a characteristic nephropathy.

The classic pathologic lesion of HIVAN is focal segmental glomerulosclerosis with collapse of the glomerular tuft, associated with dilated tubules with microcysts. Tubuloreticular inclusions, once commonly observed by electron microscopy in as many as 25% of patients, has become a rare finding, possibly owing to more effective therapy. Clinically, HIVAN patients present with heavy proteinuria and hypoalbuminemia. HIVAN patients also typically are normotensive. The absence of hypertension may be the result of a tubular defect in fluid and electrolyte handling. Ultrasound shows enlarged, echogenic kidneys. The degree of azotemia varies, but HIVAN always has been characterized by a rapid deterioration of renal function.

In early studies of the natural history of HIVAN, time from diagnosis of HIVAN to initiation of hemodialysis was reportedly from weeks to months, with most patients dead within a year. More recent data show that despite improved survival of HIV-seropositive patients in general, patients with ESRD secondary to HIVAN have higher mortality rates than those with ESRD of other causes. In a review of USRDS data from 1992 to 1997, 2-year survival was 36% for patients with HIVAN compared with 64% for all other patients with ESRD. HIVAN initially was believed to be a late manifestation of acquired immune deficiency syndrome because it appeared in patients with low CD4

counts and a history of opportunistic infections. There are now reported cases, however, of HIVAN developing in patients at the time of seroconversion, indicating that it also may present early in the course of HIV.[38,39]

Renal biopsy examinations of patients have shown both proliferative and apoptotic changes. The primary process is uncertain, but because kidneys are enlarged, proliferation is most likely the predominant process.

Transforming growth factor-β (TGF-β) is a fibrogenic cytokine that regulates human immune function and has been shown to regulate HIV replication. A study of human kidneys found increased deposition of matrix proteins and increased levels of TGF-β in those kidneys with HIVAN compared with normal kidneys and with kidneys with thin basement membrane and minimal change nephropathies. This was true even when compared with kidneys of HIV infected individuals without HIVAN.[40]

In a study comparing HIV transgenic mice with normal mice, transgenic kidneys had increased basic fibroblast growth factor (bFGF) and a greater number of bFGF binding sites. Transgenic tubular epithelial cells were found to express bFGF and transgenic epithelial cells or nontransgenic cells treated with bFGF exhibited an increased rate of proliferation compared with controls.[41]

Renal mesangial cell cultures incubated in sera collected from HIV-seropositive patients showed a greater degree of proliferation than those cells incubated in normal

control sera. This effect was concentration dependent, and was inhibited in the presence of azidothymidine

Renal epithelial cells of transgenic mice[42] and biopsy specimens from a human subject with HIVAN[43] showed an increased expression of markers of proliferation such as the Ki-67 antigen, and a decreased expression of markers of differentiation such as synaptopodin.

Collapsing Glomerulopathy or Malignant FSGS:

Collapsing glomerulopathy, also known as collapsing FSGS or malignant FSGS, initially was described as a distinct clinicopathologic entity in 1986, when Weiss et al[44] reported a group of 6 patients with nephrotic syndrome, rapidly progressive renal failure, and glomerular collapse. Renal biopsy examination displayed the characteristic features of collapsing glomerulopathy: segmental and global collapse of the glomerular capillaries, wrinkling and retraction of the glomerular basement membrane, and marked hypertrophy and hyperplasia of podocytes. Tubulointerstitial changes also were prominent and included tubular dilatation and degeneration, epithelial necrosis, and interstitial fibrosis and edema. In this initial report, all 6 patients were black, and all presented with nephrotic syndrome and varying degrees of renal insufficiency. Five of the 6 patients also had a nonspecific febrile illness before presentation, but no clear etiologic factor was identified.

Most cases of collapsing glomerulopathy are either HIV-associated or idiopathic. In addition, a secondary cause of collapsing glomerulopathy is treatment with high-dose pamidronate, a bisphosphonate used to treat osteolytic bone lesions and hypercalcemia of malignancy. In 2001, 7 patients who were white, HIV negative, and developed collapsing glomerulopathy after treatment of multiple myeloma or breast cancer with pamidronate were reported. Patients were treated with pamidronate for 15 to 48 months before renal biopsy examination, and 5 of the 7 had received more than the recommended dosage of 90 mg intravenously per month. All patients developed renal insufficiency and nephrotic syndrome, with a mean creatinine level of 3.6 mg/dL and a mean 24-hour urinary protein excretion of 12.4 g/d. Three of 5 patients in whom pamidronate was withdrawn had stabilization of their renal function.[45] The same group later reported a case of collapsing glomerulopathy in which the patient's proteinuria significantly decreased after withdrawal of pamidronate but then worsened with reintroduction of this agent.[75] Since the original report of 7 patients, 10 additional cases of pamidronate-associated collapsing glomerulopathy have been seen.[46] Other centers also have reported cases of FSGS and collapsing glomerulopathy after treatment with pamidronate.[47,48]

Recent studies and case reports have suggested an association between collapsing glomerulopathy and parvovirus B19 infection.[49] This association is intriguing given the establishment of HIV as a viral cause of collapsing glomerulopathy and the frequent reports of a nonspecific febrile illness before the development of collapsing glomerulopathy. One study of 40 patients by Tanawattanacharoen et al[19] reported a significantly greater prevalence of parvovirus B19 DNA by using polymerase chain

reaction in patients with idiopathic FSGS and collapsing glomerulopathy compared with patients with membranous nephropathy and minimal change disease. A second study by Moudgil et al[50] analyzed biopsy specimens of 23 patients with collapsing glomerulopathy for parvovirus B19 DNA by using polymerase chain reaction and compared the results with biopsy specimens of classic FSGS, HIVAN, and controls with other renal diseases. Parvovirus B19 DNA was detected in 78.3% of biopsy specimens with collapsing glomerulopathy. This data suggest that infection of renal epithelial cells by parvovirus B19 may be an etiology of collapsing glomerulopathy in susceptible patients.

Glomerular visceral epithelial cell injury underlies the pathogenesis of collapsing FSGS. Podocyte injury is characterized by increased cell turnover and reversion to an immature state. In a study of 8 patients with collapsing glomerulopathy, Bariety et al[51] showed that podocytes detach from the GBM, lose their normal podocyte markers (vimentin, podocalyxin, and CR1), and acquire macrophage-associated epitopes (KP1, PG-M1, and M 18). Barisoni et al[52] studied the expression of podocyte maturity markers (WT-1, CALLA, C3b receptor, GLEPP-1, podocalyxin, synaptopodin) and the proliferation marker Ki-67 in 10 cases of idiopathic collapsing glomerulopathy, 8 cases of HIVAN, 5 cases of membranous nephropathy, and 5 cases of minimal change disease. In patients with idiopathic collapsing FSGS and HIVAN (but not in patients with other glomerular diseases), decreased expression of podocyte markers of maturity and increased expression of Ki-67 was observed. This data suggests that both idiopathic collapsing glomerulopathy and HIVAN are associated with a dysregulated, cycling podocyte phenotype.

In collapsing glomerulopathy, expression of cyclin A (a positive cell cycle regulatory protein) is increased while expression of synaptopodin, cyclin D1, and the negative cell cycle regulatory proteins p27 and p57 are decreased.[53] Shankland et al[54] evaluated a series of 9 patients with collapsing glomerulopathy, 16 patients with HIVAN, and 37 patients with other causes of nephrotic syndrome. Expression of p27 and p57 was uniformly decreased in collapsing glomerulopathy, cellular FSGS, and HIVAN.

Clinical Presentation and Course:

FSGS presents with nephrotic syndrome, defined variably by the classic tetrad of proteinuria, hypoalbuminemia, edema, and hypercholesterolemia, or by the presence of edema and nephrotic-range proteinuria.. However, a significant number of patients present with isolated proteinuria or with proteinuria and hematuria. The cause of proteinuria is uncertain. As is true for minimal change nephrotic syndrome (MCNS), proteinuria in FSGS occurs without apparent disruption of the glomerular filtration barrier sufficient to account for the massive protein loss. Both MCNS and FSGS are described as showing decreased staining for glomerular polyanion, one possible explanation for urinary loss of albumin, a negatively charged protein. Guasch et al describe a biphasic curve for glomerular permselectivity in patients with FSGS that includes decreased fractional clearance of smaller molecules, similar to what is observed in MCNS, but also increased fractional clearance of larger macromolecules, suggesting the existence of a shunt mechanism for the clearance of larger proteins. Urinary proteins may include, in addition to albumin, other components of the plasma that may have

clinical significance. These include IgG and opsonizing factors, whose loss may lead to susceptibility to infection by encapsulated bacteria; vitamin D-binding proteins and 25-OH-vitamin D_3, causing bone demineralization; and iron-binding proteins, leading to anemia.

An important consideration in the presentation of FSGS is the presence or absence of the nephrotic syndrome. In children, a survey of several studies indicates that as many as 80% of patients are nephrotic at presentation. In adults, the percentage may be somewhat lower. In a more recent retrospective study, adults were less likely to present with nephrotic syndrome than were children (55% versus 76%), but over time the incidence of nephrosis increased to greater than 80% in both groups.[23] It has been suggested that patients presenting with nephrosis are more likely to progress to chronic kidney failure. Nephrotic patients are more likely to be hypertensive, to have increased serum creatinine levels, or to have hematuria. Hypertension and azotemia also are more likely in adults than in children. Although these findings may help define a population of patients, they are not useful for determining whether a patient has FSGS or is likely to progress to renal failure. The only valid diagnostic determinant is the biopsy examination itself.

In the absence of nephrosis, FSGS may be found in as many as 30% to 50% of adult patients undergoing a biopsy procedure.[5]

The presenting feature in all patients with primary FSGS is proteinuria, frequently resulting in the nephrotic syndrome, but a nonnephrotic presentation is not unusual in up

to 25% of adults. In addition, hypertension, and renal insufficiency are common presenting features. The presentation for patients with primary FSGS may differ among the histologic variants. In contrast to patients with classic FSGS, patients with the cellular or collapsing lesion are more often black, have more advanced renal insufficiency, and more severe proteinuria at presentation.[55,56] Massive proteinuria (>10 g/d) at presentation is much more common among patients with the cellular lesion compared with patients with classic FSGS (70% versus 10% of patients).

The degree of proteinuria at presentation is one of the most important prognostic features in patients with primary FSGS.[2,4,5] Nephrotic patients with primary FSGS reach ESRD over 5 to 10 years,[4,5] and those patients with massive proteinuria (>10 g/24 h) have an even more malignant course with essentially all patients progressing to ESRD within 5 years. This is in contrast to the more favorable prognosis in patients with nonnephrotic proteinuria in whom a renal survival of over 80% is observed after 10 years.[4,6] Additionally, the level of serum creatinine at presentation is prognostic with patients having a serum creatinine level greater than 1.3 mg/dL manifesting a significantly poorer renal survival than those with a level of 1.3 mg/dL or less.[4,6] Of the various pathologic features that have been studied, the histologic feature that has most consistently been predictive of a poor prognosis is the presence of advanced (>20%) interstitial fibrosis.[6,58,59] Recent studies have now shown the presence of the cellular lesion is associated with a significantly more rapid course to ESRD than that of classic FSGS.

The presentation and course of patients with FSGS secondary to conditions

resulting from hyperfiltration or functional adaptations such as reflux nephropathy or morbid obesity may differ somewhat from that of primary FSGS. Unlike patients with primary FSGS, those with secondary FSGS often present with a more indolent course and rarely have hypoalbuminemia and nephrotic syndrome despite having nephrotic range or even massive proteinuria.[60,61] In a series of 71 patients with obesity-related FSGS, Kambham et al[60] found that though 47% of obese patients presented with nephrotic range proteinuria only 7% had nephrotic syndrome compared with patients with primary FSGS in whom 66% of patients had nephrotic range proteinuria and 54% had nephrotic syndrome. On renal biopsy examination, patients with FSGS caused by obesity, as well as those caused by reduced nephron mass, reflux nephropathy, or sickle cell disease, were found to have glomerulomegaly (over 30% greater diameter) and less extensive foot process fusion than those patients with primary FSGS.[60-62] Finally, despite similar degrees of renal insufficiency at presentation, patients with secondary FSGS have a less rapidly progressive course with a 5-year renal survival of approximately 80% compared with 50% for patients with primary FSGS.[61]

In primary FSGS, remission of proteinuria best predicts a favorable outcome in nephrotic patients.[59,63] Less than 15% of patients entering a complete remission progress to ESRD, whereas up to 50% of persistently nephrotic patients progress to ESRD over 5 years.

Even a partial remission is associated with a less rapid decline in renal function as compared with patients in whom the nephrotic syndrome persists.[5] Unfortunately,

spontaneous remissions are rare, occurring in less than 5% of nephrotic patients with primary FSGS. However, patients receiving a course of treatment with steroids are 4 to 10 times more likely to enter a remission than untreated patients.[59] Because no clinical or histologic feature at presentation allows one to predict which patients will enter a remission, the response to a course of treatment becomes the best clinical indicator of outcome.[63]

The Southwest Pediatric Nephrology Study Group reported that a significant number of children with FSGS retained normal or near-normal function several years after diagnosis. The absence of nephrosis may be a highly favorable index of disease activity. In one study, 47% of nephrotic adults progressed to end-stage kidney disease within 10 years, whereas only 8% of patients who were not nephrotic similarly progressed.[64] Regardless of the conclusions of these studies, because patients with asymptomatic proteinuria without nephrosis subsequently may become nephrotic or progress to end-stage without becoming nephrotic, it is not possible to predict outcome confidently from the symptoms at presentation.

Treatment of FSGS:

The use of angiotensin converting enzyme inhibitors (ACEIs) and or angiotensin II receptors blockers (AIIRBs) along with good blood pressure control should be part of the therapeutic approach for all proteinuric patients with FSGS and should be considered the mainstay of therapy for patients with FSGS secondary to conditions associated with hyperfiltration and/or reduced nephron mass and those patients with nonnephrotic primary FSGS. For nephrotic patients with primary FSGS, recent experience has provided a note of optimism in the use of immunosuppressive agents in treating this

otherwise progressive glomerulopathy.

A course of steroid therapy in primary FSGS is warranted in nephrotic patients with reasonably well preserved renal function (serum creatinine levels ≤3 mg/dL) in whom it is not otherwise contraindicated. As an initial approach to treatment in adults, prednisone is given at a dose of 1 mg/kg/d (up to 80 mg) for 3 to 4 months. In the elderly (≥60 y), an initial alternate-day regimen of prednisone (1-2 mg/kg up to 120 mg) for 4 to 5 months may be prudent. In patients showing a response to treatment (ie, a remission or a ≥50% reduction in proteinuria), the dose can be slowly tapered over an additional 3 months. For patients unresponsive to the initial course of therapy, a more rapid taper, over 4 weeks, should be used to minimize further steroid exposure. Steroids should be avoided in patients with familial FSGS or FSGS secondary to hyperfiltration and/or reduced nephron mass.

One differentiating factor, with corticosteroid treatment of adults,[65] is response to therapy. Pei et al[63] found that only 42% of nephrotic adults with primary FSGS received treatment as compared with 95% of children. However, over the past 20 years a more optimistic experience has emerged with complete remission rates in excess of 30% being reported in over 80% of studies, with the majority showing complete remission rates of 40% or greater. The most obvious difference among studies was the duration of therapy because the initial dose of prednisone used was similar. The total duration of therapy in those studies with a poor response rate was 2 months or less (low-dose therapy) compared with an average of 5 to 9 months (high-dose therapy) in studies achieving high remission rates. Ponticelli et al[59] reported a complete remission in only 15% of patients

treated with steroids for less than 4 months, whereas 61% of patients treated for 4 months or more entered a complete remission. Rydel et al[64] found that, in addition to a longer overall course of treatment (5 versus 3 mo), those patients achieving a remission had received an initial period of high-dose prednisone (≥60 mg/d) for a significantly longer duration than nonresponders (median time of 3 versus 1 mo, respectively). Thus, the initial duration of high-dose treatment may be as important as the overall duration of therapy. Less than one third of adults who achieve a complete remission do so by 8 weeks of therapy. The median time to complete remission is 3 to 4 months, with the majority of patients reaching a complete remission by 5 to 9 months from the beginning of treatment.[4,23,63] Based on this experience, it has now been proposed that steroid resistance in adults be defined as the persistence of the nephrotic syndrome after a 4-month trial of therapy with prednisone at a dose of 1 mg/kg/d.

Cytotoxic agents along with steroids have been used as initial therapy in approximately 20% of adults, but this appears to confer no added benefit in attaining a complete remission when compared with steroids alone. However, their use may induce a more stable remission than steroids alone.

There are essentially no data regarding the use and/or benefit of steroids in nonnephrotic patients with primary FSGS. Owing to the more favorable course in these patients a more conservative approach is preferable and consider steroid only if the patient becomes nephrotic.

Familial forms of FSGS are known to be steroid resistant and thus, steroids are of little value in these patients. In patients with secondary FSGS caused by hyperfiltration and/or reduced nephron mass (especially in patients with obesity), steroids have no place in the management of these patients and should be avoided because the risk would be greater than any potential benefit. Additionally, they may exacerbate the underlying disease (particularly in obesity-related FSGS) and accelerate the progression of renal disease.

In children, Arbus et al noted 3 clinical patterns after corticosteroid treatment of FSGS. Those who responded to steroids fared well, but those who never responded, or who developed resistance to treatment within 18 months, had a poorer prognosis. Other factors associated with greater likelihood of progression include hypertension, interstitial inflammation and fibrosis, or African-American or Hispanic ethnicity. Massive proteinuria has been associated with progression of steroid-resistant nephrotic syndrome, although the pathogenetic significance of the proteinuria remains unresolved.

Ponticelli et al.[66] have performed the prospective trial in which patients were randomized to cyclosporine (CSA) or supportive therapy only. Their definition of resistant was, however, only 6 weeks of prednisone therapy. Their age group was mixed, with both children and adults included in the study. They received CSA for 6 months at full dose and in those that had either a partial or complete remission the drug was continued but the dose was tapered to zero over 6 months. Fifty-seven percent of their treated patients had either a partial or complete remission and approximately 40% of

these were still in remission at 2 years of follow-up evaluation although the details separating their FSGS from their minimal change patients was incomplete in the published article. The highest rate of remission was in a recent study by Lee et al. However, the level of evidence was only 4, given that it was a descriptive study and there were only 5 patients with the biopsy specimen-proven diagnosis of FSGS. Even in this group with 80% initial remission, relapse was high at 50% after 1 year off drugs.

Al-Lehbi et al[67] administered mycophenolate (MMF) to 10 patients with FSGS who were resistant to steroids and were either cyclosporine dependent or resistant. Patients received MMF 1.5-2 g/d plus prednisone for a total of 6 months. There was only a mild decrease of proteinuria from 12.6 to 10.8 g/d. All patients were still nephrotic at the end of treatment. Matalon et al[68] administered MMF to 11 adults with FSGS and nephrotic syndrome, at a mean dose of 1,275 mg/d, for a mean period of 28 weeks. The treatment induced a reduction in proteinuria from 6.8 to 5.7 g/d, which was statistically significant but of little clinical relevance. In no patients did proteinuria decrease to a level below 2.5 g/d.

Choi et al[69] reported the outcome for 18 patients with FSGS dependent or resistant to corticosteroids or cyclosporine, or with progressive renal insufficiency. Twelve patients had renal insufficiency and 9 had nephrotic syndrome. These patients received MMF at initial doses of 1 to 1.5 g/d for at least 3 months, plus variable doses of steroids in 12 of them. The 24-hour urine protein to creatinine ratio significantly decreased from 2.7 to 0.8 (median 48%) at the end of the MMF treatment. Among the 9 nephrotic

patients 1 had a complete remission and 4 had a partial remission. Median serum creatinine level increased from 1.9 to 2.2 mg/dL. In the 12 patients receiving concomitant steroid therapy, prednisone could be stopped completely without relapse in 8 cases. One patient relapsed and steroid treatment was resumed, and 3 others continued on low-dose steroid treatment. MMF generally was well tolerated

Ginsburg and Dau[70] obtained a dramatic decrease in proteinuria, from 8.8 to 2.0 g/ 24 hr, and in serum creatinine level, from 2.9 to 1.0 mg/dL, in an adult patient with resistant FSGS and severe nephrotic syndrome, treated for 18 months with weekly plasmapheresis combined with moderate doses of prednisone and azathioprine. Mitwalli et al[71] reported the outcome of 11 adult patients with FSGS resistant to prolonged immunosuppression who were treated with plasmapheresis in a mean of 17 sessions over a period of 15 to 25 weeks, in combination with oral prednisolone 60 to 80 mg daily, and intravenous cyclophosphamide, 5 to 10 mg/kg monthly, for 6 months. Eight patients responded to plasmapheresis with a stabilization of renal function, associated with a long-lasting complete remission in 6 patients (54.5%) and a partial remission in 2 other patients (18.2%). The remaining 3 patients who did not respond to plasmapheresis developed progressive renal insufficiency and 2 of them reached end-stage renal failure. No severe side effects were noted in any of the studied patients. Feld et al[72] treated 8 steroid-resistant adults with 6 plasmapheresis sessions over 2 weeks. Proteinuria decreased in 2 patients, although only transiently in 1 of the 2 patients. Both the responders had stable renal function at the last follow-up evaluation. In contrast, 4 of the 6 nonresponders had a progressive decline of renal function or were receiving dialysis

treatment. No relationship between the circulating permeability factor and the development of remission was observed. Haas et al[73] assessed the effects of immunoadsorption on proteinuria and the predictive value of the permeability factor in serum measured with glomerular volume variation in 5 adults with FSGS. Immunoadsorption reduced proteinuria by more than 50% in 2 of 5 patients. In one responder the glomerular volume variation test, which was positive before treatment, became negative after the first immunoadsorption cycle. The other 4 patients had negative glomerular volume variation test results both before and after immunoadsorption.

Kidney transplantation is associated with 2 problems that are relatively specific for FSGS. One of these is recurrence related to the presence of a circulating factor that enhances glomerular permeability.[74] In children with FSGS in whom pre-emptive transplantation has been attempted to avoid hemodialysis, a very high incidence of perioperative complications has been noted. These have been attributed to graft loss from thrombosis and may represent an effect of the nephrotic state rather than of FSGS per se. For this reason, most pediatric centers now choose to dialyse all children with FSGS for a period of time before proceeding to transplant, using either coagulation studies or an index of active nephrosis such as lipid abnormalities or serum albumin to determine whether the likelihood of thrombotic complications has diminished.

Aims:

1. To identify risk factors at diagnosis associated with progression of adult

primary focal and segmental glomerulosclerosis

2. To determine survival rates based on the factors identified

The biopsy reports and case records of all patients with FSGS (n=574) diagnosed at the Christian Medical College Vellore between January 1994 to December 2003 were reviewed. The criteria that define primary FSGS are (1) A lesion involving only some of the glomeruli in the biopsy with others remaining uninvolved (2) the involved glomeruli having a segment that has undergone collapse of capillaries with obliteration of capillary lumen with or without adhesion and (3) no pathologic evidence for primary disease that might produce secondary sclerosis (i e immune complex mediated glomerulopathy). [64]

Inclusion Criteria:

a. Patient with Primary focal and segmental glomerulosclerosis

b. Age ≥16 years

c. With ≥ 3 months of follow up after diagnosis

d. Glomerular filtration rate (GFR) by Modification of Diet in Renal Disease (MDRD) formula of ≥ 10 ml / min at presentation.

Exclusion Criteria:

a. Patients with evidence of systemic disease, other disease associated with glomerulopathy, or a history of vesicouretric reflux, nephrectomy, solitary kidney, or intravenous drug abuse

b. Age < 16 years

c. GFR (by MDRD) < 10ml/min at presentation

d. Follow-up of < 3 months.

Among the secondary condition which lead to FSGS, 39 patients had history of prolonged hypertension before developing proteinuric illness, 5 patients had renal agenesis, 5 patients had underlying vesicoureteric reflux, 2 patients were morbidly obese and 4 patients had past history of nephrectomy were excluded.

Based on these criteria, a total of 343 patients were identified and formed the basis of the present study.

Study design:

Patients were first divided into two groups based on the amount of proteinuria at the time of presentation, n=182, with proteinuria ≥3 grams per day and n=161, proteinuria <3 grams per day. Nephrotic patients were subdivided on the basis of their serum albumin. Group 1 (n=117, with serum albumin <2.5 gram per dl) and Group 2 (n= 65, with serum albumin ≥2.5 grams/dl). Groups 1 and 2 were further analysed on the basis of their decline in GFR as progressor (≥10 ml/min/year) and non-progressor (<10 ml/min/year).

Clinical Parameters:

Clinical and laboratory reports were collected for each patient at the time of presentation. Nephrotic range proteinuria was defined as ≥3 gm/24 hours. Non nephrotic patients had proteinuria <3 gm/24 hours. Hypoalbuminemia was defined as serum albumin of <2.5 gm/dl. Hematuria was defined as >5 red blood cells per high-power field. Patients diastolic blood pressure ≥90 mm of Hg or a systolic blood pressure ≥140 mm of Hg were considered hypertensive. Renal failure has been defined as GFR (MDRD) <60 ml/min and GFR <10ml/min or the need of renal replacement therapy has

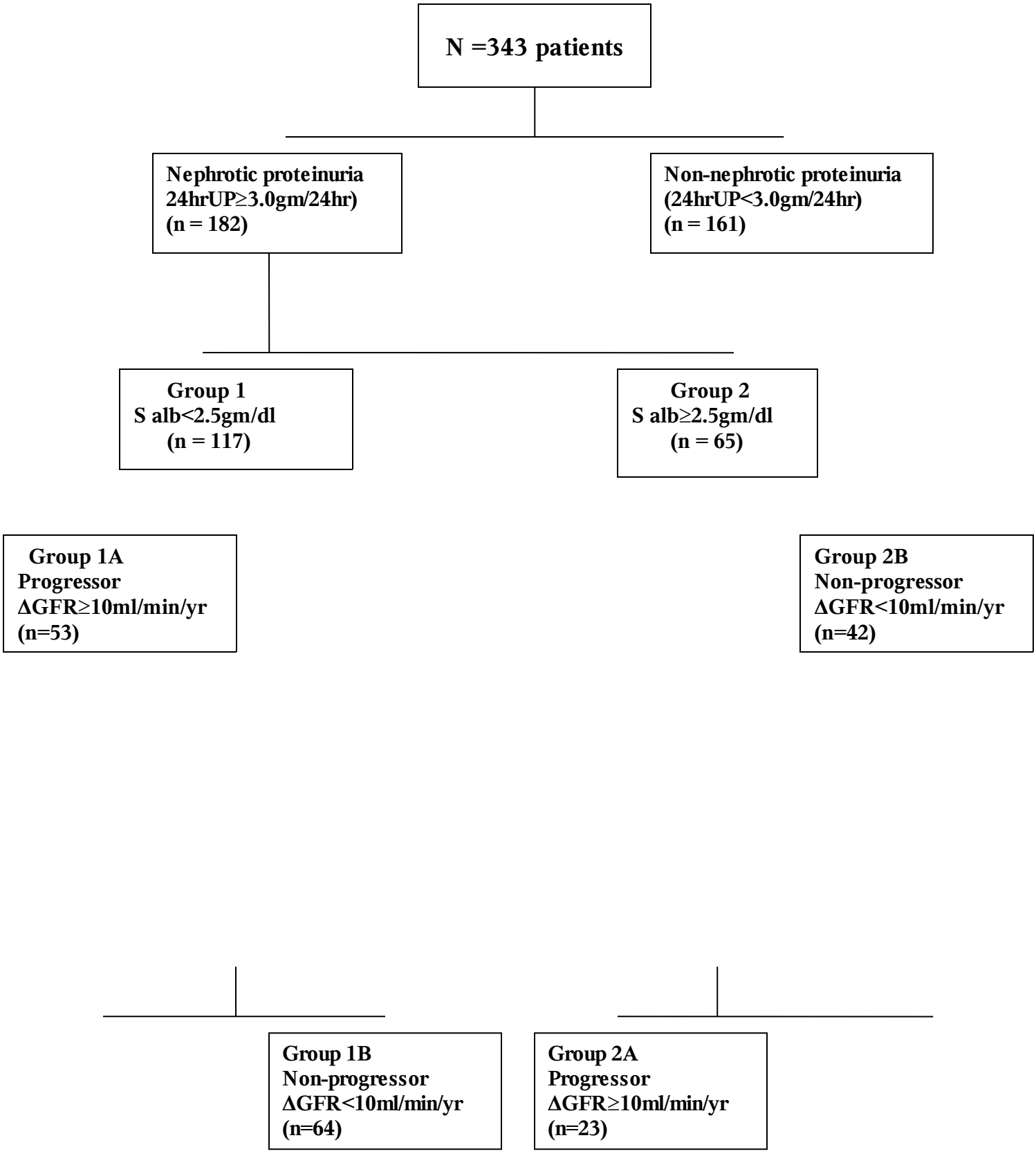
been taken as end stage renal disease.

Histopathological Parameters:

In addition to histopathological diagnosis of FSGS the other features recorded were proportion of glomeruli with segmental scars and or global scars. In addition specific histopathological changes such as mesangial hypercellularity, interstitial fibrosis, tubular atrophy and vascular involvement were evaluated according to semi-quantitative methods as absent, mild to moderate and severe. The immunofluorescence study included the following antisera conjugated with fluorescein isothiocyanate: IgG, IgM, IgA, C3. For logistic regression analysis, absent and mild was given a value of 0, and moderate to severe, a value of 1.

Statistical Analyses:

Between group comparisons for continuous variables independent t-test for normal data and Mann Whitney test for non-normal data were used. Pearson Chi-Square test was used for categorical variables. Logistic regression analysis (step-wise method) was carried out to find the factors associated with progression in both the groups (1A vs 1B and 2A vs 2B). Multivariate analyses were done on the factors whose Univariate logistic regression test had a p value of <0.25. Renal survival was calculated using the Kaplan-Meier method, and compared by Log rank test. All analyses were carried out using SPSS version 11.5.


N =343 patients
Nephrotic proteinuria
24hrUP≥3.0gm/24hr)
(n = 182)
Non-nephrotic proteinuria
(24hrUP<3.0gm/24hr)
(n = 161)
Group 1
S alb<2.5gm/dl
(n = 117)
Group 2
S alb≥2.5gm/dl
(n = 65)
Group 1A
Progressor
ΔGFR≥10ml/min/yr
(n=53)
Group 2B
Non-progressor
ΔGFR<10ml/min/yr
(n=42)
Group 1B
Non-progressor
ΔGFR<10ml/min/yr
(n=64)
Group 2A
Progressor
ΔGFR≥10ml/min/yr
(n=23)

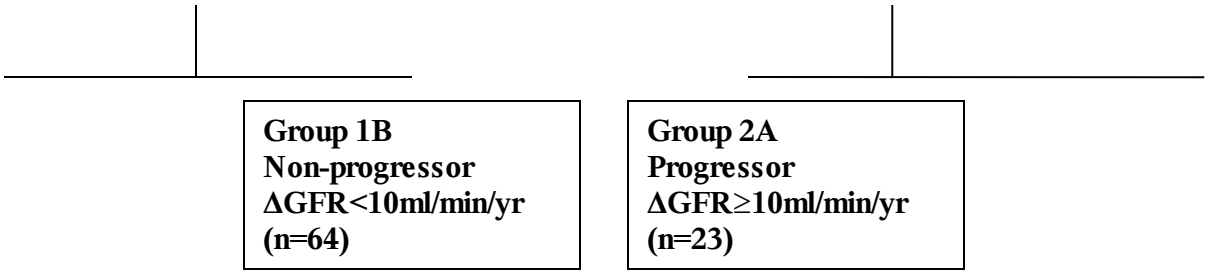


Figure 1- Study design

Table 1 summarises the demographic profile of 343 patients at the time of diagnosis. The population was predominantly male (76.4%) and the mean age at presentation was 35.3 (±13) years. At presentation nephrotic range proteinuria was seen in 53.1% patients while 40.5% had microscopic hematuria, 64.1% had hypertension and 62.4% had renal failure. The mean serum creatinine and 24 hour urine protein were 2.0 (±1.2) mg per dl and 4.3 (±3.9) grams per day respectively. The mean duration from onset of symptoms to renal biopsy was 17.2 (± 17.1) months and the duration of follow-up ranged from 3 to 120 months with a mean duration of 21.5 (±19.9) months.

Table 1: Demographic profile at diagnosis n=343

Variable	%	Mean ± SD	Median (range)
Males	76.4		
Nephrotic syndrome	53.1		
Hypertension	64.1		
Micro hematuria	40.5		
Renal failure (GFR<60ml/min)	62.4		
Age (years)		35.3±13	35 (16 – 77)
Duration of follow up (months)		21.5±19.9	12 (3 – 120)
MAP (mmHg)		103.5±12	103.3 (70 – 167)
Serum creatinine (mg/dl)		2.0±1.2	1.7 (0.6 – 6.5)
24 hr urine protein gm/d		4.3±3.9	3.2 (0.04 – 23.1)
Serum albumin (gm/dl)		3.0±1.2	3.3 (0.9-5.2)
Serum cholesterol (mg/dl)		297.6±167.2	236 (90-1200)
GFR (ml / min) at presentation		55.0±32.6	47.1 (10.1 – 125)

Nephrotic and Non-nephrotic Patients (Table 2):

Nephrotic range proteinuria was seen in 53.1% patients. Nephrotic patients were significantly younger as compared with the non-nephrotic patients (32.7±13.7 vs 38.2±11.4 years; p=0.000) and had significantly better renal function at presentation as compared to non-nephrotic (serum creatinine 1.9±1.1 vs 2.2±1.2 mg/dl; p=0.013). Nephrotic and non-nephrotic patients were similar with respect to gender, hypertension, hematuria, and duration of follow-up. Although the rate of decline in GFR was significantly higher in nephrotic patients as compared to non-nephrotic (7.1±36 vs 2.1±26 ml/min/year; p=0.000), the mean GFR of nephrotic patients at the time of presentation

was significantly higher as compared to non-nephrotic patients (61.9±33.3 vs 47.3±30.2 ml/min; p=0.000). It was noticed that the interval from the onset of symptoms to renal biopsy was significantly less in nephrotic as compared with non-nephrotic patients (14.8±15.6 vs 19.9±18.3 months; p=0.000).

Comparison of Histology:

The number of patients having moderate to severe tubular atrophy (36.3 vs 24.2%; p=0.016) and interstitial fibrosis (36.8 vs 24.2%; p=0.012) were significantly higher in nephrotic patients as compared to non nephrotic.

Table 2: Clinical, laboratory findings and histopathological characteristics at biopsy: nephrotics vs non-nephrotics

Variable	Nephrotic N=182	Non-nephrotic N=161	p
Age (years)	32.7±13.7	38.2±11.4	0.000
Males (% of patient)	80.8	71.4	NS
Duration of symptoms(months)	14.8±15.6	19.9±18.3	0.000
Follow-up (months)	20.5±21.4	22.7±19.1	NS
Hypertension(%)	60.4	68.3	NS
Mean arterial pressure (mm of Hg)	102.4±11.7	104.7±12.3	NS
Urine protein (gms/day)	7.1±3.5	1.2±0.8	0.000
Micro hematuria (%)	45.1	35.4	NS
Scr at presentation (mg%)	1.9±1.1	2.2±1.2	0.013

GFR at presentation (ml/min)	61.9±33.3	47.3±30.2	0.000
Renal failure at presentation(%)	51.1	75.2	0.000
Decline in GFR (ml/min/yr)	7.1±36	2.1±26	0.000
Serum albumin (gm/dl)	2.4±1.0	3.8±0.8	0.000
Serum cholesterol (mg/dl)	377.7±168.9	219.1±122.9	0.000
Segmental sclerosis (>50%)	9.9	6.2	NS
Moderate and severe interstitial fibrosis (%)	36.8	24.2	0.012
Tubular atrophy (%)	36.3	24.2	0.016
Vascular involvment (%)	52.2	64.6	NS
IgM deposition (%)	50.5	35.4	0.005
C3 deposition (%)	53.8	52.2	NS

Univariate analyses of factors associated with progression in nephrotic patients with low albumin (Subgroup 1A, 1B) (Table-3):

Risk factors for progression by univariate analysis in nephrotic patients with low albumin at diagnosis included the amount of proteinuria per day (9.0±2.6 vs 7.0±4.1 grams per day; p=0.000) and moderate to severe tubular atrophy (56.6% vs 23.4%; p=0.000) and interstitial fibrosis (66.0% vs 18.8%; p=0.000)

Univariate analyses of factors associated with progression in nephrotic patients with normal albumin (Subgroup 2A, 2B) (Table-3):

Risk factors for progression by univariate analysis in nephrotic patients with

normal albumin group at diagnosis included amount of proteinuria per day (7.7 ±.2.7 vs 4.7±2.3) grams per day; p=0.000) and moderate to severe tubular atrophy (52.2% vs 21.4%;p=0.011) and interstitial fibrosis (60.9% vs 14.3%;p=0.000)

Table 3: Clinical, laboratory findings and histolopathological characteristics of nephrotic patients at biopsy: progressor vs non-progressor

Variable	Subgroup 1A(n=53)	Subgroup 1B(n=64)	p	Subgroup 2A(n=23)	Subgroup 2B(n=42)	p
Age (years)	33.1±16.7	33.1±13.9	NS	30.1±11.1	33.0±10.4	NS
Males (% of patient)	73.6	85.9	NS	82.6	81.0	NS
Duration of symptoms till biopsy (months)	11.0±11.1	19.6±20.9	0.000	7.7±4.7	16.1±12.5	0.000
Follow-up (months)	17.7±15.4	22.2±26.1	NS	17.1±16.8	23.2±22.3	NS
Hypertension (%)	54.7	56.3	NS	69.6	69.0	NS
MAP (mm of Hg)	101.9±14.0	101.7±9.8	NS	103.3±13.9	103.7±9.8	NS
24 hours urine protein (gms/day)	9.0±2.6	7.0±4.1	0.000	7.7 ±.2.7	4.7±2.3	0.000
Microhematuria (%)	41.4	51.6	NS	60.9	31.0	NS
S cr at presentation	1.4±0.6	2.1±1.2	0.001	1.6±1.1	2.1±1.3	NS
Renal failure at presentation (%)	35.8	62.5	0.004	39.1	59.5	NS
GFR at presentation (ml/min)	71±28.7	55.6±33.7	0.005	70.9±35.1	55.0±34.5	NS
S cholesterol (mg/dl)	454±160.5	448.4±149	NS	297.5±170	234±61.3	NS
Segmental sclerosis (>50%)	13.2	7.8	NS	13.0	7.1	NS
Moderate and severe interstitial fibrosis (%)	66.0	18.8	0.000	60.9	14.3	0.000

Tubular atrophy (%)	56.6	23.4	0.000	52.2	21.4	0.011
Vascular involvment (%)	45.3	50.0	NS	65.2	57.1	NS
IgM deposition (%)	52.8	50.0	NS	56.5	45.2	0.025
C3 deposition (%)	43.4	53.1	NS	47.8	64.3	NS

Multivariate Logistic regression analyses of factors associated with progression:

Risk factors for progression by multivariate analysis in nephrotic patients with low albumin (table-4) at diagnosis (group 1A,1B) included amount of proteinuria (β 0.001), and moderate to severe interstitial fibrosis (Odds Ratio 8.5). In nephrotic patients with normal albumin (table-5) at diagnosis (group 2A,2B), the amount of proteinuria (β 0.001), and moderate to severe interstitial fibrosis (Odds Ratio 6.1) were significant risk factors.

Table 4: Multivariate analysis of prognostic factors: low albumin (group 1)

Variable	**β**	**Odds ratio**	**95.0 % C.I.**		**p value**
			Lower	**Upper**	
Proteinuria	0.001	1.000	1.000	1.100	0.041
Interstitial fibrosis	2.141	8.504	3.377	21.417	0.000
Renal failure at presentation	-1.275	0.279	0.113	0.694	0.006
Constant	-1.495	0.224			0.013

All factors satisfied 25 % level of significance in Univariate analysis

Table 5: Multivariate analysis of prognostic factors: normal albumin (group 2)

Variable	β	Odds ratio	95.0 % C.I. Lower	Upper	p value
Proteinuria	0.001	1.000	1.000	1.001	0.004
Interstitial fibrosis	1.824	6.198	1.635	23.498	0.007
Constant	-3.563	0.028			0.000

All factors satisfied 25 % level of significance in Univariate analysis

Multivariate analysis of risk factors for progression to ESRD (logistic regression model) (Table 6):

A multivariate analysis examined the risk factors for progression to ESRD of the entire nephrotic cohort (both low and normal albumin) as compared with the non-nephrotic cohort. Patients with moderate to severe interstitial fibrosis had the highest risk of progression (Odds Ratio 8.3;95% CI 4.6,15.0). Nephrotics with low albumin have higher risk of progression (Odds Ratio 4.3; 95% CI 2.2,8.3) than

nephrotics with normal albumin (Odds Ratio 3.1;95% CI 1.4,6.9). Renal failure at presentation did not emerge as a risk factor for progression (O 0.3;95% CI 0.1,0.6).

Table 6: Multivariate analysis of risk factors for progression to ESRD:
(Logistic regression model)

Factors	β	SE	Exp(B)	95.0% CI Lower	Upper	p
Nephrotic+Low albumin	1.46	0.33	4.32	2.23	8.37	0.000
Nephrotic+Normal albumin	1.15	0.39	3.17	1.46	6.90	0.003
Moderate and severe interstitial fibrosis	2.12	0.30	8.36	4.64	15.05	0.000
Renal failure at presentation	-1.07	0.30	0.34	0.19	0.61	0.000
Constant	-1.97	0.33	0.13			0.000

Renal Survival Rates:

Kaplan-Meier analysis showed that cumulative probability of renal survival from the onset of symptoms was 105 months (95% CI; 91,120). Mean renal survival for the patient in the progressor category was significantly low (48 months, 95% CI; 38,58) as compared with the patients in non-progressor category (122 months, 95% CI; 110,134 p=< 0.001).

The mean renal survival in patients who had moderate to severe interstitial

fibrosis is significantly low as compared to absent or mild interstitial fibrosis (49 and 133 months: p=<0.0001). Patients with no risk factors (proteinuria and interstitial fibrosis) had a mean renal survival time of 90 (95% CI:84,97) months while the mean renal survival time in those with both risk factors were 46 (95% CI:35,57, p=0.002) months.

In all, 44 patients (12.8%) had reached ESRD at last follow-up.

Figure 2 - Cumulative probability of renal survival vs risk factors: progressor vs non-progressor

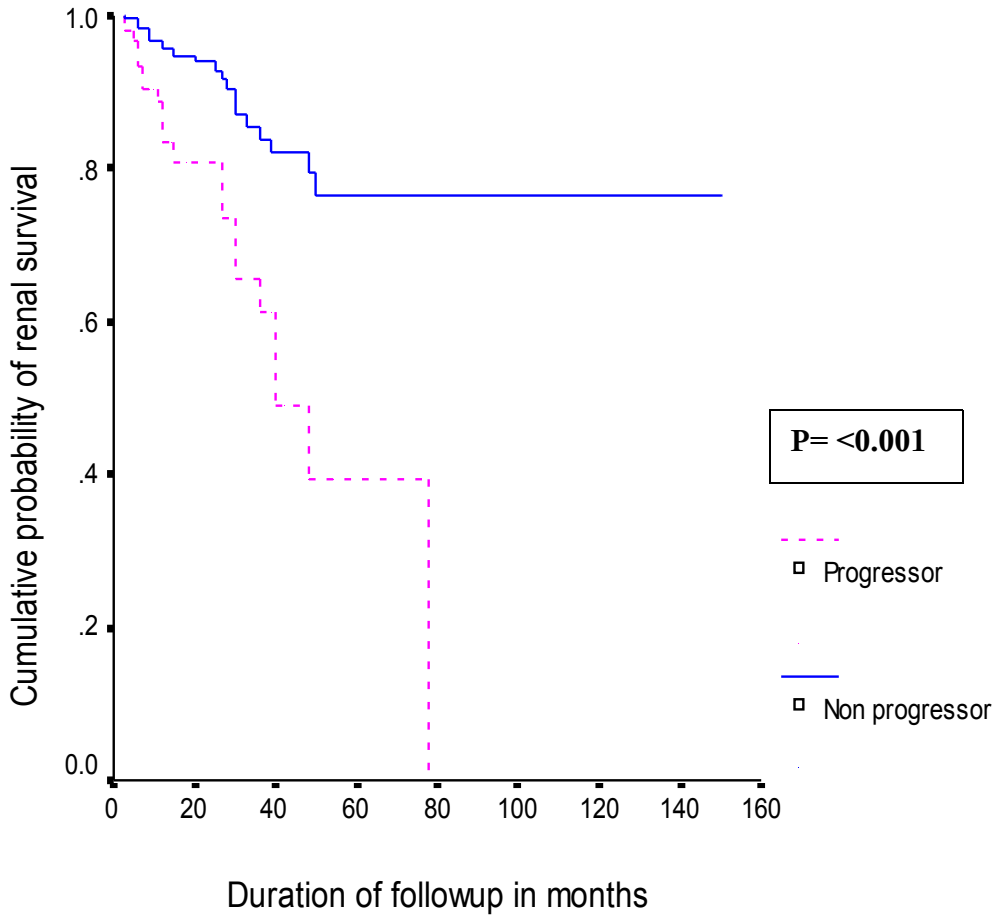


Fig **on-**

nep

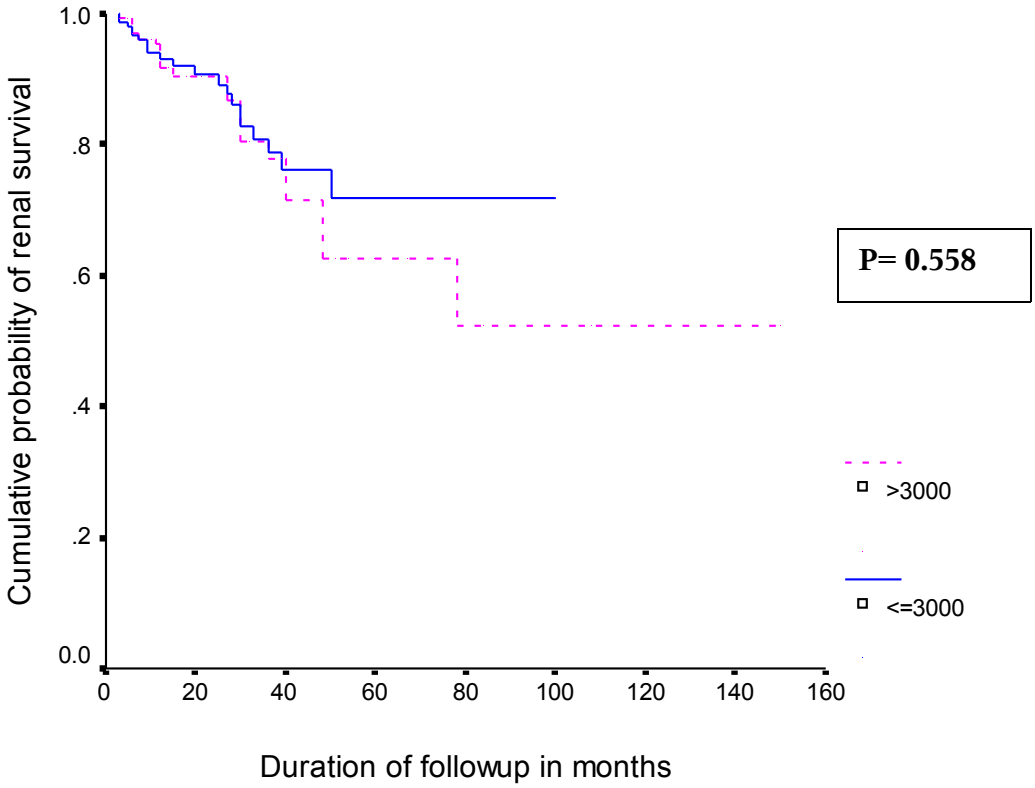


Figure 4 - Cumulative probability of renal survival vs risk factors: degree of interstitial fibrosis

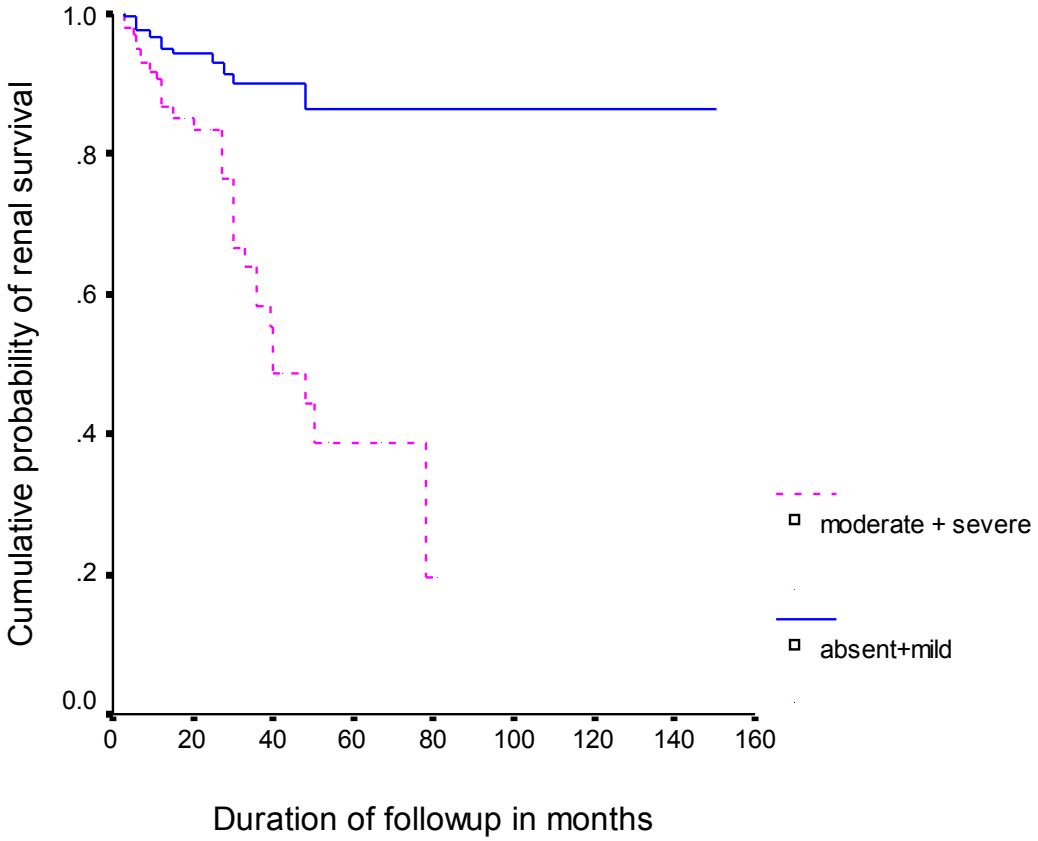
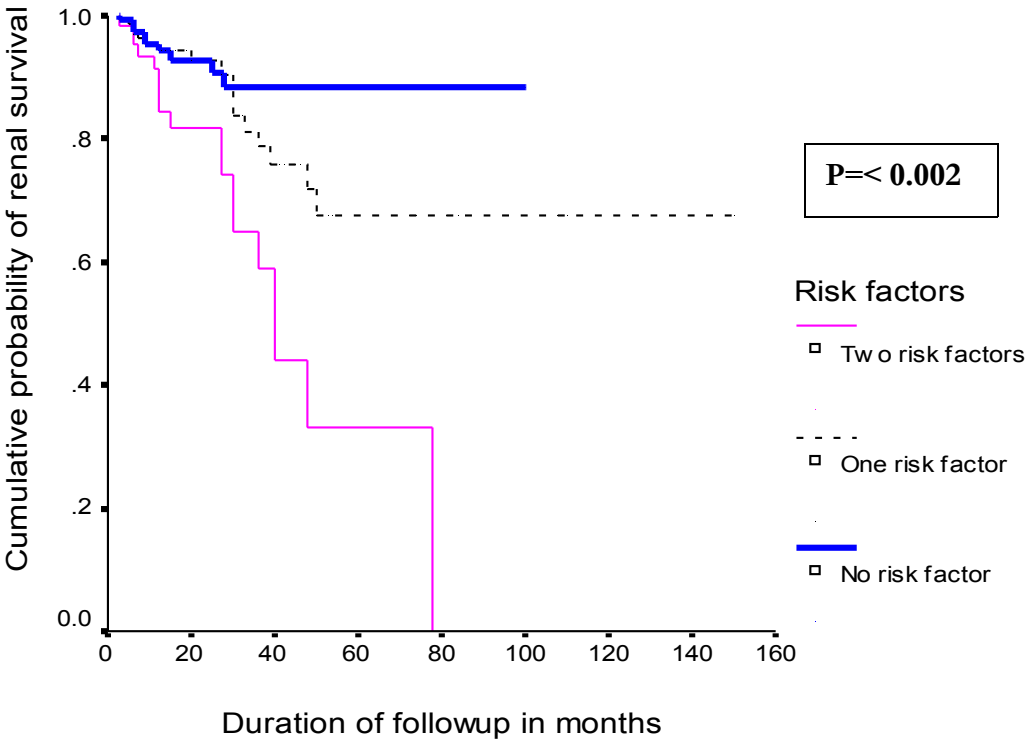

Cumulative probability of renal survival
1.0
.8
.6
.4
.2
0.0
0
20
40
60
80
100
120
140
160
Duration of followup in months
moderate + severe
absent+mild

Figure 5 - Cumulative probability of renal survival : additive risk



Primary FSGS is a major cause of proteinuria and nephrotic syndrome in adults, the etiology of which is largely unknown. There are very few reported studies on adult FSGS from India.[65,75]

In the study by Agarwal et al[65], 65 adults with biopsy proven FSGS were followed (mean duration 32 months). Nephrotic syndrome (81%) was the commonest mode of presentation. All patients received steroids for an average duration 8-12 weeks before a response to steroid is clearly catergorised. Complete and partial remission developed in 31% and 27% of the cases, respectively. They concluded that response to steroids can not be predicted clinically at the time of presentation and all patients should be given one course of steroids as patients who respond to steroids have better long term survival.

Pokhariyal et al[75] in a retrospective analysis of 93 adult patients with biopsy proven FSGS followed up for a mean duration of 12.6 months, showed that hypertension, hematuria and degree of proteinuria did not significantly affect the response to steroid therapy. Univariate logistic regression analysis showed that the significant factors predictive of remission were duration of steroid therapy, serum creatinine at onset and presence of interstitial fibrosis (>25%) at initial biopsy. Multivariate logistic regression analysis showed that the only factor predictive of remission was steroid therapy duration >16 weeks. They concluded that patients with idiopathic FSGS required treatment for at least 16 weeks, before labeling them as steroid non-responsive. Patients with interstitial fibrosis (>25%) have a significantly poor response to therapy.

In this study we analysed a large cohort of adult patients of primary FSGS with regard to the natural course, renal survival and the risk factors that affect it.

Nephrotic range proteinuria was seen in 53.1 percent of patients at the time of presentation which is comparable with that reported by Cattran et al.[23] and York et al (55%)[76]. Although hypertension (64.1%) was the commonest mode of presentation in our cohort, nephrotic syndrome was the commonest mode of presentation in the two studies, Agarwal et al (81%) and Pokhariyal et al (59%) reported from India. This could be because 62.4% of our patients had renal failure at presentation compared to 19% by Agarwal et al and 26% by Pokhariyal et al.

The nephrotic patients were significantly younger at presentation. At the time of presentation, nephrotics had higher GFR as compared to non-nephrotic patients but the rate of decline in GFR was significantly higher in nephrotics. The time from the onset of symptoms to presentation was significantly shorter in the nephrotics. The nephrotics presented earlier with oedema when they still had better preserved renal function.

Even among nephrotics, analysed on the basis of serum albumin at diagnosis, the amount of proteinuria and the degree of interstitial fibrosis and tubular atrophy on biopsy are the significant risk factors for progression. None of the other histopathological characteristics like percentage of glomeruli with segmental sclerosis, degree of mesangial hypercellularity, degree of vascular involvement, degree of IgM or C3 deposits predicted progression, as has been shown earlier[5].

On multivariate analysis, factors independently predictive of outcome were the amount of proteinuria and the degree of interstitial fibrosis in both groups as shown earlier[5]. Rydel et al[64] and Pei et al[57] were unable to demonstrate proteinuria as an independent predictor of progression perhaps due to the unusually high rate of remission in their treated nephrotic patients. However when patients entering a remission were

eliminated from their multivariate analysis, proteinuria became prognostically significant. Contrary to other studies, renal failure at presentation was not a predictor of progression to ESRD in our cohort. This is because the high risk nephrotics presented earlier as swelling appeared even when the renal function was preserved.

The 10 year renal survival was 60% which is in concordance with previous reports from the west.[2,5,23]

This study confirms that tubulointerstitial fibrosis and amount of proteinuria as significant risk factors for the progression of primary FSGS in adults. However renal failure at presentation was offset by the rapidly progressing nephrotic patients presenting earlier and with preserved renal function.

In this study therapeutic response has not been taken into account since only the risk factors at presentation are examined. Studies have confirmed that a therapeutic response by prolonged course of steroids with remission of proteinuria changes the natural history of FSGS.[4,7] However, some studies have shown that therapeutic response can't be predicted at presentation[7,64] and uniform protocol with careful follow-up is required to document comparable remission rates.

Conclusions:

1. Clinical and pathological indicators help to predict renal failure in adult primary FSGS at the time of presentation.

2. Independent predictors of disease progression are

    a. amount of proteinuria

    b. degree of interstitial fibrosis

3. Independent predictors of development to ESRD in adult primary FSGS are

    a. nephrotic range proteinuria

    b. low serum albumin

    c. degree of interstitial fibrosis

4. Renal failure at presentation is not a predictor of progression could be because of high risk nephrotics presented earlier as swelling appeared even when the renal function was preserved.

5. This study predict the probability of renal survival in adult primary FSGS at presentation and therefore identify high risk group.

Bibliography:

1. Narsimhan B, Chacko B, John GT, Korula A, Kirubakaran MG, Jacob CK: Characterization of kidney lesions in Indian adults: towards a renal biopsy registry. *J Nephrol 19(2): 205-10, 2006.*

2. Cameron JS, Turner DR, Ogg CS, Chantler C, Williams DG: The long-term prognosis of patients with focal and segmental glomerulosclerosis. *Clin Nephrol 10: 213-218, 1978.*

3. Beaufils H, Alphonse JC, Guedon J, Legrain M: Focal glomerulosclerosis: Natural history and treatment. A report of 70 cases. *Nephron 21: 75-85, 1978*.

4. Korbet SM, Schwartz MM, Lewis EJ: The prognosis of focal segmental glomerulosclerosis of adulthood. *Medicine (Baltimore) 65:304-311, 1986*.

5. Wehrmann M, Bohle A, Held H, Schumm G, Kedziorra H, Pressler H: Long-term prognosis of focal sclerosing glomerulonephritis. An analysis of 250 cases with particular regard to tubulointerstitial changes. *Clin Nephrol 33: 115-122, 1990*.

6. Valeri A, Barisoni L, Appel G, Seigle R, D'Agati V: Primary collapsing focal glomerulosclerosis: A clinicopathologic study. *Kidney Int 50: 1734-1746, 1996.*

7 Schwartz MM, Korbet SM, Rydall J, Borok R, Genchi R: Primary focal segmental glomerulosclerosis in adults: Prognostic value of histologic variants. *Am J Kidney Dis 25: 845-852, 1995.*

8. Hayslett JP, Krassner LS, Bensch KG, et al: Progression of "lipoid nephrosis" to renal insufficiency. *N Engl J Med 281:181-187, 1969.*

9. Churg J, Habib R, White RH: Pathology of the nephrotic syndrome in children: A report for

the International Study of Kidney Disease in Children. *Lancet 760:1299-1302, 1970.*

10. Fogo A, Glick AD, Horn SL, et al: Is focal segmental glomerulosclerosis really focal? Distribution of lesions in adults and children. *Kidney Int 47:1690-1696, 1995.*

11. D'Agati V: The many masks of focal segmental glomerulosclerosis. *Kidney Int 46:1223-1241, 1994.*

12. Schwartz MM, Evans J, Bain R, et al: Focal segmental glomerulosclerosis: Prognostic implication of the cellular lesion. *J Am Soc Nephrol 10:1900-1907, 1999.*

13. Valeri A, Barisoni L, Appel GB, et al: Idiopathic collapsing focal segmental glomerulosclerosis: A clinicopathologic study. *Kidney Int 50:1734-1746, 1996.*

14. Detwiler RK, Falk RJ, Hogan SL, et al: Collapsing gloemerulopathy: A clinically and pathologically distinct variant of focal segmental glomerulosclerosis. *Kidney Int 45:1416-1424, 1994.*

15. Korbet SM, Genchi RM, Borok RZ, et al: The racial prevalence of glomerular lesions in nephrotic adults. *Am J Kidney Dis 27:647-651, 1996.*

16. Haas M, Meehan SM, Karrison TG, et al: Changing etiologies of unexplained adult nephrotic syndrome: A comparison of renal biopsy findings from 1976-1979 and 1995-1997. *Am J Kidney Dis 30:621-631, 1997.*

17. Ingulli E, Tejani A: Racial differences in the incidence and renal outcome of idiopathic focal segmental glomerulosclerosis in children. *Pediatr Nephrol 5:393-397, 1991.*

18. Kopp JB: Renal dysfunction in HIV-1-infected patients. *Curr Infect Dis Rep 4:449-460, 2002.*

19. Tanawattanacharoen S, Falk RJ, Jennette JC, et al: Parvovirus B19 DNA in kidney tissue of

patients with focal segmental glomerulosclerosis. *Am J Kidney Dis 35:1166-1174, 2000.*

20. Li RM, Branton MH, Tanawattanacharoen S, et al: Molecular identification of SV40 infection in human subjects and possible association with kidney disease. *J Am Soc Nephrol 13:2320-2330, 2002.*

21. Barisoni L, Valeri A, Radhakrishnan J, et al: Focal segmental glomerulosclerosis: A 20-year epidemiological perspective. *J Am Soc Nephrol 5:347A, 1994.*

22. Haas M, Spargo BH, Coventry S: Increasing incidence of focal-segmental glomerulosclerosis among adult nephropathies: A 20-year renal biopsy study. *Am J Kidney Dis 26:740-750, 1995.*

23. Cattran DC, Rao P: Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. *Am J Kidney Dis 32:72-79, 1998*.

24. Conlon PJ, Butterly D, Albers F, et al: Clinical and pathologic features of familial focal segmental glomerulosclerosis. *Am J Kidney Dis 26:34-40, 1995.*

25. Holzman LB, St. John PL, Kovari IA, et al: Nephrin localizes to the slit pore of the glomerular epithelial cell. *Kidney Int 56:1481-1491, 1999.*

26. Demmer L, Primack W, Loik V, et al: Frasier syndrome: A cause of focal segmental glomerulosclerosis in a 46,XX female. *J Am Soc Nephrol 10:2215-2218, 1999.*

27. Denamur E, Bocquet N, Mougenot B, et al: Mother-to-child transmitted WT1 splice-site mutation is responsible for distinct glomerular diseases. *J Am Soc Nephrol 10:2219-2223, 1999.*

28. Schumacher V, Scharer K, Wuhl E, et al: Spectrum of early onset nephrotic syndrome associated with WT1 missense mutations. *Kidney Int 53:1594-1600, 1998.*

29. Shalhoub RJ: Pathogenesis of lipoid nephrosis: A disorder of T-cell function. *Lancet 2:556-560, 1974.*

30. Hoyer JR, Vernier RL, Najarian JS, et al: Recurrence of idiopathic nephrotic syndrome after renal transplantation. *J Am Soc Nephrol 12:1994-2002, 2001.*

31. Zimmerman SW: Increased urinary protein excretion in the rat produced by serum from a patient with recurrent focal glomerular sclerosis after renal transplantation. *Clin Nephrol 22:32-38, 1984.*

32. Artero ML, Sharma R, Savin VJ, et al: Plasmapheresis reduces proteinuria and serum capacity to injure glomeruli in patients with recurrent focal glomerulosclerosis. *Am J Kidney Dis 23:574-581, 1994.*

33. Savin VJ, Sharma R, Sharma M, et al: Circulating factor increasing glomerular permeability in recurrent focal segmental glomerulosclerosis. *N Engl J Med 334:878-883, 1996.*

34. Dantal J, Bigot E, Bogers W, et al: Effect of plasma protein adsorption on protein excretion in kidney transplant recipients with recurrent nephrotic syndrome. *N Engl J Med 330:7-14, 1994.*

35. Savin VJ, Sharma R, Lovell HB, Welling DJ: Measurement of albumin reflection coefficient with isolated rat glomeruli. *J Am Soc Nephrol 3: 1260-1269,1992.*

36. Olson JL, Hostetter TH, Rennke HG, et al: Altered glomerular permselectivity and progressive sclerosis following extreme ablation of renal mass. *Kidney Int 22:112-126, 1982.*

37. Rao TK, Filippone EJ, Nicastri AD, et al: Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. *N Engl J Med 310:669-673, 1984.*

38. Levin ML, Palella F, Shah S, et al: HIV-associated nephropathy occurring before HIV antibody seroconversion. *Am J Kidney Dis 37:E39, 2001.*

39. Winston JA, Bruggeman LA, Ross MD, et al: Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *N Engl J Med 344:1979-1984, 2001.*

40. Yamamoto T, Noble NA, Miller DE, et al: Increased levels of transforming growth factor-beta in HIV-associated nephropathy. *Kidney Int 55:579-592, 1999.*

41. Ray PE, Bruggeman LA, Weeks BS, et al: bFGF and its low affinity receptors in the pathogenesis of HIV-associated nephropathy. *Kidney Int 46:759-772, 1994.*

42. Barisoni L, Bruggeman LA, Mundel P, et al: HIV-1 induces renal epithelial dedifferentiation in a transgenic model of HIV-associated nephropathy. *Kidney Int 58:173-181, 2000.*

43. Winston JA, Bruggeman LA, Ross MD, et al: Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *N Engl J Med 344:1979-1984, 2001.*

44. Weiss MA, Daquioag E, Margolin EG, et al: Nephrotic syndrome, progressive irreversible renal failure, and glomerular “collapse”: A new clinicopathologic entity? *Am J Kidney Dis 7:20-28, 1986.*

45. Markowitz GS, Appel GB, Fine PL, et al: Collapsing focal segmental glomerulosclerosis following treatment with high-dose pamidronate. *J Am Soc Nephrol 12:1164-1172, 2001.*

46. Markowitz GS, Fine PL, D'Agati VD: Nephrotic syndrome after treatment with pamidronate. *Am J Kidney Dis 39:1118-1122, 2002.*

47. Lockridge L, Papac RJ, Perazella MA: Pamidronate-associated nephrotoxicity in a patient with Langerhans's histiocytosis. *Am J Kidney Dis 40:E2, 2002.*

48. Barri YM, Sukumalchantra S, Munshi NC, et al: Pamidronate-induced FSGS in patients

with multiple myeloma. *J Am Soc Nephrol 12:92A, 2001.*

49. Moudgil A, Shidban H, Nast CC, et al: Parvovirus B19 infection-related complications in renal transplant recipients: Treatment with intravenous immunoglobulin. *Transplantation 64:1847-1850, 1997.*

50. Moudgil A, Nast CC, Bagga A, et al: Association of parvovirus B19 infection with idiopathic collapsing glomerulopathy. *Kidney Int 59:2126-2133, 2001.*

51. Bariety J, Nochy D, Mandet C, et al: Podocytes undergo phenotypic changes and express macrophagic-associated markers in idiopathic collapsing glomerulopathy. *Kidney Int 53:918-925, 1998.*

52. Barisoni L, Kriz W, Mundel P, et al: The dysregulated podocyte phenotype: A novel concept in the pathogenesis of collapsing idiopathic focal segmental glomerulosclerosis and HIV-associated nephropathy. *J Am Soc Nephrol 10:51-61, 1999.*

53. Barisoni L, Mokrzycki M, Sablay L, et al: Podocyte cell cycle regulation and proliferation in collapsing glomerulopathies. *Kidney Int 58:137-143, 2000.*

54. Shankland SJ, Eitner F, Hudkins KL, et al: Differential expression of cyclin-dependent kinase inhibitors in human glomerular disease: Role in podocyte proliferation and maturation. *Kidney Int 58:674-683, 2000.*

55. Detwiler RK, Falk RJ, Hogan SL, et al: Collapsing gloemerulopathy: A clinically and pathologically distinct variant of focal segmental glomerulosclerosis. *Kidney Int 45:1416-1424, 1994.*

56. Korbet SM, Schwartz MM: Primary focal segmental glomerulosclerosis: A treatable lesion with variable outcomes. *Nephrology 6:47-56, 2001.*

57. Pei Y, Cattran D, Delmore T, Katz A, Lang A, Rance P: Evidence suggesting undertreatment in adults with focal segmental glomerulosclerosis. Regional Glomerulonephritis Registry Study. *Am J Med. 1987 May;82 (5):938-44.*

58. Schwartz MM, Korbet SM, Rydel JJ, et al: Primary focal segmental glomerular sclerosis in adults: Prognostic value of histologic variants. *Am J Kidney Dis 25:845-852, 1995.*

59. Ponticelli C, Villa M, Banfi G, et al: Can prolonged treatment improve the prognosis in adults with focal segmental glomerulosclerosis? *Am J Kidney Dis 34:618-625, 1999.*

60. Kambham N, Markowitz GS, Valeri AM, et al: Obesity-related glomerulopathy: An emerging epidemic. *Kidney Int 59:1498-1509, 2001.*

61. Praga M, Morales E, Herrero JC, et al: Absence of hypoalbuminemia despite massive proteinuria in focal segmental glomerulosclerosis secondary to hyperfiltration. *Am J Kidney Dis 33:52-58, 1999.*

62. Falk RJ, Scheinman J, Phillips G, et al: Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. *N Engl J Med 326:910-915, 1992.*

63. Pei Y, Cattran D, Delmore T, et al: Evidence suggesting under-treatment in adults with idiopathic focal segmental glomerulosclerosis. *Am J Med 82:938-944, 1987.*

64. Rydel JJ, Korbet SM, Borok RZ, et al: Focal segmental glomerular sclerosis in adults: Presentation, course and response to treatment. *Am J Kidney Dis 25:534-542, 1995.*

65. Agarwal SK, Dash SC, Tiwari SC, et al: Idiopathic adult focal segmental glomerulosclerosis: A clinicopathological study and response to steroids. *Nephron 63:161-171, 1993.*

66. Ponticelli C, Rizzoni G, Edefonti A, et al: A randomized trial of cyclosporine in steroid-

resistant idiopathic nephrotic syndrome. *Kidney Int 1377-1384, 1993.*

67. Al-Lehbi MA, Al-Mutairi KA, Al-Meshari OI, et al: Mycophenolate mofetil (MMF) in steroid resistant focal segmental glomerulosclerosis (FSGS) (cyclosporine dependent or resistant). *J Am Soc Nephrol 10:94A, 1999.*

68. Matalon A, Valery A, Appel GB: Treatment of focal segmental glomerulosclerosis. Semin *Nephrol 20:309-317, 2000.*

69. Choi MJ, Eustace JA, Gimenez LF, et al: Mycophenolate mofetil treatment for primary glomerular diseases. *Kidney Int 61:1098-1114, 2002.*

70. Ginsburg DS, Dau P: Plasmapheresis in the treatment of steroid-resistant focal segmental glomerulosclerosis. *Clin Nephrol 48:282-287, 1997.*

71. Mitwalli AH: Adding plasmapheresis to corticosteroids and alkylating agents: Does it benefit patients with focal segmental glomerulosclerosis? *Nephrol Dial Transplant 13:1524-1528, 1998.*

72. Feld SM, Figueroa P, Savin V, et al: Plasmapheresis in the treatment of steroid-resistant focal segmental glomerulosclerosis in native kidneys. *Am J Kidney Dis 32:230-237, 1998.*

73. Haas M, Godfrin Y, Oberbauer R, et al: Plasma immunadsorption treatment in patients with primary focal and segmental glomerulosclerosis. *Nephrol Dial Transplant 13:2013-2016, 1998.*

74. Sharma M, Sharma R, Reddy SR, et al: Proteinuria after injection of human focal segmental glomerulosclerosis factor. *Transplantation 73:366-372, 2002.*

75. Pokhariyal S, Gulati S, Prasad N, Sharma RK, Singh U, Gupta RK, Mittal S, Mehta B: Duration of optimal therapy for idiopathic focal segmental glomerulosclerosis. *J Nephrol 16(5):691-696, 2003.*

Proforma

SL. NO.

NAME **AGE** **SEX : M/F**

HOSP NO. **DOFV** **DOLV**

DURATION OF SYMPTOMS

PAST HISTORY

1. **RECURRENT UTI**
2. **HYPERTENSIOIN**
3. **RENAL DISEASE**
4. **NEPHRECTOMY**
5. **CONGENITAL HEART DISEASE**
6. **MEDICATIONS**
7. **OBESITY**
8. **RENAL AGENESIS**

CLINICAL FEATURES

1. **ANEMIA**
2. **EDEMA**
3. **BLOOD PRESSURE**
4. **SYSTEMIC EXAMINATION**

FOLLOW-UP

Months	Hb	TC	24 HR UPRO	UREA	CREAT	S ALB	S CHO
0							
3							

6							
9							
12							
15							
18							
21							
24							
27							
30							

URINE ANALYSIS **BLOOD SUGAR AC/PC**

HbsAg **HIV** **HCV**

USG ABDOMEN

RENAL BIOPSY

BIOPSY NO.

TOTAL NUMBER OF GLOMERULI

PROPORTION OF GLOMERULI WITH SEGMENTAL SCAR

PROPORTION OF GLOMERULI WITH GLOBAL SCAR

DEGREE OF TUBULAR ATROPHY

DEGREE OF INTERSTITIAL FIBROSIS

DEGREE OF VASCULAR INVOLVMENT

IMMUNOFLUORESCENCE STUDY

OUTCOME

S. CREATININE < 10ML/MIN AT LAST FOLLOW-UP

RENAL REPLACEMENT THERAPY

DURATION OF RENAL SURVIVAL FROM FIRST SYMPTOMS

DURATION OF RENAL SURVIVAL FROM BIOPSY